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THE PROTECTIVE ROLE OF ROYAL JELLY AGAINST CHOLESTEROL-ENRICHED DIET AS A RISK FACTOR FOR DEVELOPING CARDIAC AND HEPATIC DISORDERS IN RATS

El-kholy, W.M[1]., Abdel-Wahhab, M.A[2]., El-Nekeety, A.A[2] and Amra, H.A[2]

[1]Zoology Dept., Faculty of Science, Mansoura Univ., Mansoura, Egypt.
[2]Food Toxicology & Contaminants Dept. National Research Center, Dokki, Cairo, Egypt.

ABSTRACT

The present study aims to evaluate the protective effects of royal jelly (RJ) against the hypercholesterolemia as a risk factor for developing cardiac and hepatic disorder in rats.

Results showed that feeding rats on high cholesterol diet (HCh-D) increased significantly the serum, heart and liver total lipids, total cholesterol (T.Ch), triglycerides (TG) and total phospholipid as well as serum LDL-C and LDL-C/HDL-C ratio, this is in contrast to a significant decrease in serum HDL-C and HDL-C/T.Ch ratio. The results also revealed significant elevation in serum, cardiac and hepatic AST, ALT, ALP and LDH as well as serum and cardiac CK activities. In addition, HCh-D elevated significantly the lipid peroxidation product malondialdehyde (MDA) while decreased significantly glutathione (GSH) content and superoxide dismutase (SOD) activity in both the cardiac and hepatic tissues. Animals received RJ alone were comparable to the controls in most of the parameters tested expect significant increase in HDL-C and HDL-C/T.Ch ratio and significant decrease in LDL-C/T.Ch ratio in serum. This is in addition to significant increase in SOD activity in cardiac tissue and in GSH content in hepatic tissue. The administration of RJ for 4 and 6 weeks to rats fed on HCh-D resulted in significant improvement in all the tested parameters towards the normal values. However, these beneficial effects of RJ were more pronounced in the animals treated for 6 weeks. In conclusion, RJ has a protective effect against hypercholesterolemia and hence the risk of developing cardiac or hepatic disorders, this protection was time dependent.

Key wards: Royal jelly- cholesterol- heart- liver – hypercholesterolemia.

INTRODUCTION

Cholesterol in limited amount is important for the regulation of certain body functions. but high level of cholesterol in blood forms fatty deposition in the arteries **[Schwartz *et al.*, (2001)]**. These depositions may cause coronary heart disease that is of the most common cause of death in the world **[Marasas, (2001)]**. Hypercholesteramia is a major risk factor for atherosclerosis which is the most common of the human arteriopathies that cause intimal thickening **[Seidel, (1993)]**. Cholesterol burden. closely related to a continuous high-cholesterol diet (HCh-D) impairs coronary endothelial nitric oxide synthase (eNOS) activity in small vessels. as well as in conduit vessels through formation of complexes of eNOS protein and inhibitory caveolin **[Cooper & Heagerty, (1998)]**. Coronary microvascular eNOS dysfunction impairs the regulation of coronary flow and mitochondrial respiration **[Xie *et al.*, (1996)]** and promotes inflammatory cell infiltration **[Hoshida *et al.*, (1999) and Koyanagi *et al.*, (2000)]**. Moreover the role of free radical reaction and lipid peroxidation in experimental hyperlipidemia has been suggested in the pathomechanism of fatty liver **[Blazovics *et al.*, (1993) and Festi *et al.*, (2004)]** which is associated with hydroxyl radical formation **[Tseng *et al.*, (1996)]**.

Royal jelly (RJ) is one of the natural products secreted from hypopharangeal and mandibular glands of nurse worker bees (*Apis mellifera L*). It contains many important compounds with antioxidant and many other biological activities, such as free amino acids, proteins, sugars, fatty acids mainly 10-hydroxy-2-decenoic acid; (10-HDA). minerals (mainly iron and calcium) and vitamins (mainly thiamine, niacin, riboflavin) **[Karaali *et al.*, (1988) and Bloodworth *et al.*, (1995)]**.

Royal jelly has broad spectrum of biological and pharmacological properties such as antibacterial **[Fujiwara *et al.*, (1990)]** anti-inflammatory **[Fujii *et al.*, (1990)]** anticancer **[Tamura *et al.*, (1987) and Wu & Liu, (1991)]** antioxidant **[Takeshi *et al.*, (2001)]** and antimicrobial effects **[Pollet *et al.*, (2002)]**. Furthermore, it has been found that 10-HAD; one of the most important components of RJ have hypolipidemic effect **[Vittek, (1995)]** and immunomodulatory action **[Oka *et al.*, (2001)]** as well as vasodilative and hypotensive activity **[Shinoda *et al.*, (1978)]**. Therefore, the present study was undertaken to demonstrate the possible protective effects of royal jelly against feeding

cholesterol enriched diet and the associated risks of developing cardiac and hepatic disorders in rats as a laboratory animal model.

MATERIALS AND METHODS

Experimental Animals:-

Three-month old Sprague-Dawley male rats (100-120 g) purchased from animal house colony Giza, Egypt, were maintained on standard lab diet (protein: 160.4; fat: 36.3 and fiber 41g/kg) and free access to water. They were kept in wire cages and housed in a room free from any source of chemical contamination, artificially illuminated and thermally controlled, at the Animal House Lab., National Research Centre, Dokki, Cairo, Egypt.

Experimental Design:-

After an acclimatization period of one week, thirty rats were divided into five groups (6 rats each) as follows: group 1, untreated control; group 2, treated orally with RJ (100 mg/kg b.w); group 3, fed high cholesterol diet for 6 weaks (0.5% w/w) according to **[Moussavi *et al.*, (1989)]**; group 4, fed high cholesterol diet alone for 2 weeks followed by concomitant supplementation of RJ for other 4 weeks (treatment effect); group 5, fed high cholesterol diet plus RJ at the same time for 6 weeks (protective effect).

Chemicals:

All reagents used were of the highest purity available. Cholesterol (*purity* >99%) was purchased from Winlab Leicestershire LE 169 E J U.K. Kits for estimating total lipids, total cholesterol, triglycerides, phospholipids and high density lipoprotein were purchased from pointe Scientific Inc. (USA). Lactate dehydrogenase (LDH), transaminases (ALT & AST), and alkaline Phosphatase (ALP) kits were obtaineded from BioMérieax SA (France). Creatine kinase kit was obtained from Stanbio Laboratory, Inc. (San Antonio, Texas, USA). Malondialdehyde (MDA), glutathione (GSH) and superoxide dismutase (SOD) chemicals were obtained from Eagle diagnostics, HAS.

Production and Preparation of RJ:

The production of RJ was occurred in Meet- Ghamr region. It is well known that the methods of producing royal jelly are similar to those

of rearing queen bees, but in case of production of royal jelly; larvae are removed during their larval period to extract the royal jelly which found beneath them. Thus the obtained fresh RJ (1g) was dissolved in 100 ml distilled water and 1 ml of the solution was given to rats by dose (1ml /100 g b.w) equal according to **[Vittek (1995)]**.

Sampling:-

At the end of experimentation period (6 wks), blood samples were collected from all animals from reto-orbital venous plexus, in chilled nonheparinized tubes, which were centrifuged at 3000 rpm for 10 min at 4 °C the sera were separated and kept frozen at - 20°C. The animals then were sacrificed, known parts of the liver and heart were removed, cleaned, accurately weighed and homogenized (Potter-Elvhjem) in 10 - fold volume of ice cold (20 mM) Tris- HCl buffer (pH 7.4). This homogenate was centrifuged at 1700 rpm at 4°C for 10 min and the supernatant was stored at -20°C until analysis.

Biochemical Assay:-

The following biochemical methods were performed: Total lipids **[Zollner & Kirsch, (1962)]**; total cholesterol **[Charles & Richmond, (1974)]**; triglycerides **[Wahlefeld, (1974)]**; phospholipid **[Baginiski *et al.*, (1972)]**; HDL- cholesterol **[Assmann, (1979)]**; and LDL-cholesterol **[Friedewald *et al.*, (1972)]**. The activities of lactate dehydrogenase **(Tietz, 1987)**; creatine kinase **[Szasz, (1976)]**; ALT and AST **[Reitman & Frankel, (1957)]** and alkaline phosphatase **[Roy, (1970)]**. Lipid peroxidation was estimated by the measurement of malondialdehyde (MDA) **[Esterbauer et al., (1991)]**. Glutathione content (GSH) was determined spectrophotometerically by the method of **[Prins & Loose (1969)]**. Superoxide dismutase activity was assayed spectrophotometerically by red formazan dye reduction procedure **[Suttle, (1986)]**.

Statistical analysis:

All data were statistically analyzed using the General Linear Models Procedure of the Statistical Analysis System **[SAS, (1982)]**. The significance of the differences among treatment groups was determined by ANOVA fallowed by Waller-Duncan k-ratio **[Waller & Duncan, (1969)]**. All statments of significance were based on probability of $P \leq 0.05$.

RESULTS

Lipid profile in the Serum, Heart and Liver Organs:-

The effects of RJ on total lipids in the serum, heart and liver organs, presented in table (1). Feeding with high cholesterol diet (HCh-D) resulted in a significant increase in the total lipids in serum, heart and liver. RJ alone had no significant effects on total lipids in serum, heart or liver. Treatment with RJ for 2 wks post feeding HCh-diet and concomitantly up to 4 wks succeeded to reduce the elevation observed in the serum total lipids in and mentioned tissues. Rats received RJ plus HCh- D concomitantly for 6 wks showed a significant decrease in total lipids in heart and liver compared with HCh- D group. Moreover, total lipids in serum and liver of rats received the combined treatment for six weeks was comparable to the control.

The obtained results also indicated that rats fed on HCh-D showed higher levels of total cholesterol (T.Ch) in serum, heart and liver comparing with those of the control group. RJ alone decreased T. Ch significantly in the heart of normal rats. RJ treatment of HCh-D fed rats resulted in a significant decrease ($P \leq 0.05$) in T-Ch towards the normal values of the controls. Treatment with RJ for 6 weeks was more effective than the treatment for 4 weeks.

The effects of different treatments on Triglycerides (TG) in different treated groups are depicted in table (1). Analysis of variance showed that, rats fed HCh- D showed a significant increase ($P \leq 0.05$) in TG compared to the control. Treatment with RJ alone does not resulted in any significant change in concentration of TG in the serum, heart and liver organs. The combined treatment of RJ and HCh- D for 4 or 6 weeks resulted in a significant improvement in the concentration of TG in the serum, heart and liver organs. However, it normalized the TG level in the liver which was significantly comparable to the control at 6 weeks treatment.

The present results indicated, also, that treatment with HCh- D resulted in a significant increase in phospholipids in the serum, heart and liver tissues (Table 1). Treatment with RJ alone has no significant effects on the total phospholipids but the combined treatment of RJ and HCh- D resulted in the reduction of phospholipids in the serum, heart and liver organs relative to that treated with HCh- D, although it failed to normalize it.

Table (1): Effect of Rj on Lipid Profile in Serum, Heart and Liver of Rats Fed Normal or High Cholesterol Diet (HCh-D) for 4 and 6 Weeks.

Parameters		Control	RJ	HCh- D	HCh- D +RJ (4 wks)	RJ + HCh-D (6 wks)
Serum	Total Lipids (mg/dl)	30.70 ± 0.67 [a]	30.04 ± 0.70 [a]	59.7 ± 0.52 [b]	38.12 ± 0.51 [c]	28.08 ± 0.44 [a]
	T.Ch (mg/dl)	135.77 ± 3.92 [a]	138.77 ± 4.14 [a]	378.44 ± 4.65 [b]	258.65 ± 4.44 [c]	180.57 ± 5.72 [d]
	TG (mg/dl)	111.20 ± 1.74 [a]	110.18 ± 2.97 [a]	230.57 ± 2.57 [b]	122.64 ± 1.14 [c]	98.96 ± 4.57 [d]
	Phospholipids (mg/dl)	82.44 ± 0.71 [a]	81.26 ± 1.85 [a]	152.97 ± 4.54 [b]	70.80 ± 0.95 [c]	65.26 ± 2.69 [d]
	HDL-C (mg/dl)	62.98 ± 1.35 [a]	69.55 ± 1.53 [b]	38.92 ± 0.25 [b]	50.65 ± 1.03 [c]	60.40 ± 1.15 [c]
	LDL-C (mg/dl)	50.56 ± 4.02 [a]	49.69 ± 3.17 [a]	272.99 ± 4.76 [b]	231.93 ± 4.58 [c]	139.75 ± 5.58 [d]
	HDL/T.Ch	0.46 ± 0.02 [a]	0.50 ± 0.01 [b]	0.10 ± 0.03 [c]	0.014 ± 0.01 [d]	0.33 ± 0.02 [e]
	LDL/HDL-C	0.80 ± 0.01 [a]	0.71 ± 0.01 [b]	7.01 ± 0.12 [c]	4.58 ± 0.02 [d]	2.31 ± 0.01 [e]
Heart	Total Lipids (g/g wet tissue)	5.75 ± 0.80 [a]	5.30 ± 0.29 [a]	11.18 ± 0.17 [b]	3.73 ± 0.04 [c]	2.96 ± 0.01 [d]
	T.Ch (mg/g wet tissue)	42.28 ± 1.38 [a]	38.95 ± 2.4 [b]	286.10 ± 6.94 [c]	183.13 ± 7.66 [d]	153.84 ± 3.08 [e]
	TG (mg/g wet tissue)	72.24 ± 1.62 [a]	71.03 ± 3.98 [a]	153.73 ± 2.55 [b]	80.40 ± 1.03 [c]	77.60 ± 1.99 [d]
	Phospholipids (mg/100g dry tissue)	27.64 ± 0.52 [a]	28.96 ± 0.60 [a]	114.48 ± 4.13 [b]	88.68 ± 2.86 [c]	74.38 ± 3.32 [c]
Liver	Total Lipids (g/g wet tissue)	13.12 ± 0.82 [a]	12.55 ± 0.58 [a]	27.53 ± 0.49 [b]	10.04 ± 0.33 [a]	11.6 ± 0.4 [a]
	T.Ch (g/g wet tissue)	71.5 ± 1.95 [a]	73.41 ± 2.43 [a]	287.34 ± 25.55 [b]	244.28 ± 24.44 [c]	104.77 ± 4.02 [d]
	TG (g/g wet tissue)	78.06 ± 4.84 [a]	72.41 ± 3.84 [a]	146.48 ± 1.51 [c]	68.93 ± 0.86 [d]	78.83 ± 2.04 [a]
	Phospholipids (mg/100g dry tissue)	27.57 ± 0.95 [a]	24.23 ± 0.68 [a]	54.7 ± 2.16 [b]	20.5 ± 0.21 [c]	18.6 ± 0.15 [c]

Values were represented as means ± SE of six animals in each group
Within each row, means superscript with different letters are significantly different ($P \leq 0.05$).

Rats fed HCh- D showed a significant decrease in serum HDL-C in contrast to significant increase in LDL-C compared to the control. Rats treated with RJ alone showed significant elevation in HDL-C compared to the control group. On the other hand, rats treated with RJ and HCh- D showed significant improvement in HDL-C and LDL-C level in comparison with HCh- D fed group. This improvement was more pronounced in the group received the combined treatment for 6 weeks.

It is of interest to indicate that HDL/T.Ch ratio was significantly lower in the HCh- D group compared to the other treatment groups. However, this ratio was found to be enhanced in the group fed HCh- D and treated with RJ especially for 6 weeks. In addition, the ratio between LDL-C and HDL-C was found to be increased in rats received HCh- D only. Those received the combined treatment of HCh- D and RJ showed a significant improvement in this ratio. However, treatment for 6 weeks was more effective.

Enzymes:-

The current results, in table 2, indicated that rats fed on HCh- D showed significant higher levels of LDH activity in the serum, heart and liver tissues compared to control group. LDH activity in the serum and mentioned tissues was comparable to the control in the group received RJ alone. Rats treated with RJ and HCh- D at the two tested periods (4 and 6 wks) showed a significant reduction in LDH activity compared to normal levels. RJ treatment succeeded to decrease LDH in heart and liver tissues (4 and 6 weeks) respectively.

In the same concern, significant elevations were found between the rats fed HCh- D comparing with the control group or the RJ alone treated group regarding serum or cardiac CK activity. Meanwhile the combined treatment with RJ and HCh- D for either 4 or 6 weeks resulted in a significant enhancement in the serum and cardiac CK activity.

Rats fed HCh- D showed a significant increase in ALT and AST activities in the serum, heart and liver organs (Table 2). ALT activity in rats received RJ alone was comparable to the control group. The combined treatment of RJ plus HCh- D resulted in significant improvement in ALT activity towards the normal values. Although it did not normalize it in the group treated for 4 weeks, treatment with RJ for 6 weeks succeeded to normalize ALT and AST activities in the serum, heart and liver tissues.

Table (2): Effect of Rj on some Enzymes in Serum, Heart and Liver of Rats Fed Normal or High Cholesterol Diet (HCh-D) for 4 and 6 Weeks.

Parameters		Control	RJ	HCh- D	HCh- D +RJ (4 wks)	RJ + HCh- D (6 wks)
Serum (IU/L)	LDH	190.39 ± 1.86 [a]	198.22 ± 4.43 [a]	230.6 ± 3.57 [b]	128.72 ± 3.44 [c]	173.65 ± 2.58 [d]
	CK	400.86 ± 2.03 [a]	398.09 ± 9.85 [a]	499.72 ± 6.94 [b]	289.88 ± 13.07 [c]	260.5 ± 6.74 [d]
	ALT	44.4 ± 2.87 [a]	42.0 ± 4.50 [a]	78.2 ±1.16 [b]	51.6 ± 5.99 [c]	47.2 ± 1.36 [a]
	AST	17.0 ± 0.71 [a]	17.4 ± 1.54 [a]	32.0 ± 0.89 [b]	28.4 ± 2.91 [c]	17.8 ± 0.92 [a]
	ALP	1.96 ± 0.16 [a]	2.21 ± 0.22 [a]	5.84 ± 0.63 [b]	4.0 ± 0.63 [c]	2.81 ± 0.18 [a]
Heart (IU/g wet tissue)	LDH	15.06 ± 0.85 [a]	15.41 ± 0.33 [a]	25.62 ± 0.46 [b]	14.82 ± 0.40 [c]	13.75 ± 0.22 [c]
	CK	400.86 ± 2.03 [a]	398.09 ± 9.85 [a]	499.72 ± 6.94 [b]	289.88 ± 13.07 [c]	260.5 ± 6.74 [d]
	ALT	17.4 ± 0.67 [a]	17.6 ± 1.5 [a]	31.4 ± 1.54 [b]	24.2 ± 1.02 [c]	19.2 ± 3.12 [a]
	AST	28.58 ± 2.11 [a]	28.73 ± 2.23 [a]	32.72 ± 0.58 [b]	30.47 ± 0.84 [c]	26.71 ± 0.23 [a]
	ALP	27.64 ± 0.52 [a]	28.96 ± 0.60 [a]	114.48 ± 4.13 [b]	105.68 ± 2.86 [c]	92.38 ± 3.32 [c]
Liver (IU/g wet tissue)	LDH	33.04 ±1.25 [a]	31.5 ±0.22 [a]	42.97 ±1.87 [b]	28.86 ±0.85 [a]	29.05 ±1.98 [a]
	ALT	16.16 ± 0.46 [a]	15.82 ± 0.28 [a]	32.45 ±0.65 [b]	23.63 ± 0.22 [c]	15.56 ± 1.05 [a]
	AST	19.4 ± 1.26 [a]	20.86 ± 1.85 [a]	29.6 ± 3.30b [b]	25.2 ± 1.02 [c]	18.38 ± 2.97 [a]
	ALP	13.2 ± 0.37 [a]	13.6 ± 1.43 [a]	27.4 ± 1.16 [b]	19.6 ± 1.60 [c]	14.1 ± 1.88 [a]

Values were represented as means ± SE of six animals in each group
Within each row, means superscript with different letters are significantly different ($P \leq 0.05$).

Alkaline phosphatase (ALP) activity was significantly increased in the serum, heart and liver tissues of the rats treated with HCh- D (Table 2). However, ALP activity in rats treated with RJ alone were comparable to the control. The combined treatment of RJ plus HCh- D for 4 weeks succeeded to decrease the elevation levels of ALP activity in the serum, heart and liver tissues but did not normalize it. Moreover, the treatment with RJ plus HCh- D for 6 weeks succeeded to restore the enzyme activity in serum and liver to the normal values of the control.

Lipid peroxidation:-

Results in table (3) showed that high cholesterol diet induce an oxidative stress as indicated by the significant increase in MDA level accompanied with the significant decrease in GSH content and SOD activity. Treatment with RJ alone resulted in a significant increase in GSH and SOD accompanied with significant decrease in MDA compared to the control values. Treatment with RJ plus HCh- D resulted in a significant improvement in MDA and GSH levels and SOD activity. These effects were pronounced in the group treated for 6 weeks of RJ. Generally, the combined treatment of HCh- D and RJ resulted in a significant improvement in the antioxidant status in a time dependent fashion which was more pronounced in the group received RJ for 6 weeks.

DISCUSSION

In the current study, rats fed high cholesterol diet (HCh- D) showed significant increase in all the tested lipid parameters in the serum, heart and liver tissues (total lipids, total cholesterol, triglycerides, total phospholipids and serum LDL-C) and significant decline in the serum HDL-C. Such results are in harmony with prior researches regarding the effect of ingestion of HCh- D on serum lipid profile in rats **[Khanna *et al.*, (2002) and Devi & Sharma, (2004)]**. However, the obtained data ran parallel to the decline in HDL-C/T.Ch ratio and the elevation LDL/HDL-C ratio seen in rats fed on HCh- D. These results were in agreement with the findings of **Shyamala *et al.* (2003)** and reflect a condition of hypercholesterolemia and hyperlipidemia in response to this diet and indicate increased susceptibility to the risk of atherosclerosis **[Barcat *et al.*, (2006)]** as well as the danger of the pathogenesis of fatty liver **[Blazovics *et al.*, (2004)]**. Our results were

also supported by the findings of **Hassan *et al.* (2005)** who reported that, rats fed HCh- D showed a significant increase in LDL-C, total lipids, total cholesterol, phospholipids and Tri-G accompanied with a significant decrease in HDL-C.

Table (3): Effect of Rj on Lipid Peroxidation Product (MDA), Glutathione(GSH), Superoxide Dismutase (SOD) in Heart and Liver of Rats Fed Normal or High Cholesterol Diet (HCh-D) for 4 and 6 Weeks.

Parameters		Control	RJ	HCh- D	HCh- D +RJ (4 wks)	RJ + HCh- D (6 wks)
Heart	MDA (n.mol/ g wet tissue)	28.52 ± 0.53 [a]	29.92 ± 0.48 [a]	49.94 ± 0.45 [b]	37.75 ± 1.01 [c]	33.04 ± 0.62 [d]
	GSH (mg/ g wet tissue)	0.53 ± 0.013 [a]	0.51 ± 0.004 [a]	0.25 ± 0.013 [b]	0.39 ± 0.006 [c]	0.47 ± 0.008 [d]
	SOD (u/ g wet tissue)	26.57 ± 0.50 [a]	29.04 ± 0.65 [b]	10.22 ± 0.38 [c]	18.52 ± 0.38 [d]	22.44 ± 0.53 [e]
Liver	MDA (n.mol/ g wet tissue	35.24 ±0.61 [a]	35.51 ±0.33 [a]	99.88 ±0.49 [b]	64.93 ±1.003 [c]	46.36 ±0.57 [d]
	GSH (mg/ g wet tissue)	0.63 ± 0.010 [a]	0.70 ± 0.007 [b]	0.33 ±0.010 [c]	0.46 ± 0.012 [d]	0.56 ± 0.020 [e]
	SOD (u/ g wet tissue)	32.99 ± 1.01 [a]	32.95 ± 0.89 [a]	12.22 ± 0.43 [b]	21.83 ± 0.46 [c]	29.26 ± 0.38 [d]

Values were represented as means ± SE of six animals in each group
Within each row, means superscript with different letters are significantly different ($P \leq 0.05$).

Lipid accumulation in HCh-diet fed group can be explained by increasing the amount of triglycerides depots in the liver. Alternatively, the detectable increase in serum triglycerides may be attributed to the decreased lipase activity **[Hassan *et al.*, (2005)]**. However, hyperlipidemia is caused by lipid metabolic changes. The results, herein, may be attributed to an increase in the synthesis of fatty acids in the liver or possibly due to incidence of liver cholestosis **[Hassan *et al.*, (2005)]**. Furthermore, the observed abnormalities in lipoprotein profile may be related to the overproduction of low density lipoprotein (LDL-C) by the liver or the decrease in the removal of LDL-C from the circulation **[Tsutsumi *et al.*, (1995)]**. These results can be explained by a decrease in the cholesteryl ester (CE) import to the liver and an increase in its export from it **[Hassan *et al.*, (2005)]**.

In addition, the increased level of LDL-C and the decreased level of HDL-C, reported herein, subsequently led to an increase in the LDL-C/HDL-C ratio. Such ratio, which was considered the most important than T.Ch in the determination of the risk for developing coronary heart disease **[Muller *et al.*, (2003)]**. According to **Li *et al.* (2007)** hypercholesterolemia appears critical to the atherogenic process and tends to lead to serious cardiovascular diseases (CVD). Moreover, plasma triacylglycerols (TG) were also an independent risk factor for CVD in many epidemiological studies **[Hopkins *et al.*, (2005)]**.

On the other hand, the results of the current study indicated that adminstration of RJ to rats fed HCh-diet caused significant reductions in serum, cardiac and hepatic levels of different lipid fractions as well as in serum LDL-C and LDL/HDL-C ratio, while a significant elevation was seen in HDL-C compared to HCh- D fed rats. Similarly, **Shen *et al.* (1995)** found that RJ reduced serum cholesterol level and increased HDL-C levels. Also, **Vittek (1995)** found that treatment with RJ resulted in a significant decrease in serum and liver total lipids and total cholesterol levels and retarded the formation of atheromas in the aorta (atherosclerotic plaque) in rats and rabbits fed hyperlipidemic diet. These observations strongly supported our findings regarding the effects of RJ on decreasing HDL-C and other lipid compartments in the serum, liver and heart. These findings are also in agreement with the results stated by **Abou-Hozaifa *et al.* (1993).** The explanation of the hypolipidemic and protective effect of RJ for heart and liver tissue is its antioxidant effects **[Takeshi *et al.*, (2001) and Nagai & Inoue, (2004)]** protecting tissue from damage directly via its components such as minerals, proteins, 10

hydroxy-2- decenoic acid (10-HAD) organic acid **[Xu *et al.*, (2002)]** and vitamins or by enhancing HDL-C which has other effects beyond reverse cholesterol transport (RCT) that reduce atherosclerosis such as the antioxidant effect **[Remaley *et al.*, (2001)]**, inhibiting the oxidation of LDL-C and the decrease in nitric oxide (NO) **[Oram & Lawn, (2001)]**. HDL can also transport the enzyme paraoxonase (PON) which catalyzes the degradation of oxidized LDL phospholipids. If these oxidized phospholipids were not degraded, they could stimulate an inflammatory response and subsequent monocyte adhesion to the endothelium, accelerating atherosclerosis **[Liu *et al.*, (2003)]**. This is, in addition to the anti-thrombotic effects of HDL **[Mabuchi & Tall, (1990)]**.

Several mechanisms can be proposed for cholesterol-lowering effect of RJ: first, its content of the medium chain hydroxyl fatty acids, such as 10-HAD **[Xu *et al.*, (2002)]** and sterol **[Lercker *et al.*, (1982)]**. 10- HAD is a functional factor of preventive and therapeutic effects of RJ on hyperlipidemia **[Xu *et al.*, (2002)]**. Second, it may be attributed to increasing of fecal bile acid excretion in hypercholesterolemic rats. However RJ could become a more important contributor under certain pathological conditions; *in vitro* studies suggesting that it accounted for 50% of bile acid synthesis **[Stravitz *et al.*, (1996)]**. Third, RJ however contains 3% vitamins, such as pantothenic acid (vitamin B_5) and free amino acids **[Bloodworth *et al.*, (1995)]** which are essential for improvement of general health and homeostasis of many physiological processes. Furthermore, the observed hypolipidemic effects of RJ, in addition to its inhibition to serum levels of LDL-C and enhancing effect on HDL-C may be the reason for regression of cardiovascular adverse effects and fatty liver seen in rats fed HCh-diet **[Badimon *et al.*, (1990)]**.Our results, thus, are consistent with the previous finding showing that RJ reduces both coronary risks and total mortality and that their beneficial effects appears over a long period **[Fruchart *et al.*, (1998)]**.

The activity of serum, cardiac and hepatic AST, ALT, ALP and LDH enzymes as markers for liver or heart damage and CK as a marker for myocardium lesion. They were significantly elevated in rats fed HCh-diet compared to normal ones. The current results are in agreement with **Shyamala *et al.* (2003)** and **Hassan *et al.* (2005)** who reported that these enzymes were increased in rats fed HCh-diet. Such increase may be attributed to hyperlipidemia and oxidative stress in the liver and heart tissues as the cell membrane damage, result in the leakage of these

enzymes to the blood stream. Moreover, the elevation in the activity of LDH and CK enzymes, in both serum and cardiac tissue in rats fed HCh-D, may be attributed to a generalized increase in cardiac membrane permeability and are considered particularly useful in diagnosis of muscular dystrophy **[Doran & Wilkinson, (1975)]**. It has been found that a significant elevation in LDH and CK activities were detected in heart diseases **[Lanter, (1975)]**. However, high cholesterol diet has been found to impair coronary endothelial nitric oxide synthase (eNOS) **[Cooper & Heagerty, (1998)]** which inturn, impair the regulation of coronary flow and mitochondrial respiration **[Xie *et al.*, (1996)]** and promote inflammatory cell infiltration **[Koyanagi *et al.*, (2000)]**.

In the present work, administration of RJ to rats fed on HCh- D remarkably prevented the elevation of AST, ALT, ALP, LDH and CK activities in both serum and tissues (heart and liver). In consistant with the current results, **Ahmed *et al.* (2000)** reported that RJ administration resulted in a significant decrease in serum ALT, AST, ALP and T.Ch in alloxan-diabetic rats. In the present study, the protective effect of RJ could be partly due to their antioxidative components and to their free radical scavenging properties **[Takeshi *et al.*, (2001)]**. RJ contains large amounts of an emulsion of proteins, sugars, lipids, vitamins, enzymes, hormones and other substances in a water base **[Lercker *et al.*, (1981)]** and these compounds could prevent oxidative damage **[Abdel-Wahhab *et al.*, (2006)]** to the cardiac and hepatic tissue and hence can prevent the enzymes release. This is based on RJ-protein content, primarily on its dominant protein Apa1 **[Majtan *et al.*, (2006)]**. Sequential analysis of Apa1 showed that it contained high content of essential amino acids Arg, Leu, and Ile **[Schmitzova´ *et al.*, (1998)]**. At lower concentrations, Arg causes preferential hydration of proteins, thus, stabilizing them **[Timasheff, (2002)]** and it serves as an agent that preferentially destabilizes the incorrectly folded proteins **[Reddy *et al.*, (2003)]**.

The results, also, illustrated that HCh- diet enhanced lipid peroxidation (LP) as indicated by the significant increase in MDA level which is presumably results of free- radical- mediated damage **[Yin et al., (1998)]**. Free radicals are known to attack the highly unsaturated fatty acids of the cell membranes to induce LP which considered a key process in many pathological events and is one of the reactions induced by oxidative stress **[Schinella *et al.*, (2002)]**. Lipid peroxidation is one of the main manifestations of oxidative damage. Thus HCh- diet induced

oxidative stress may be the mechanism by which it causes many pathological events leading to heart and liver disorders.

Glutathione, one of the members of the antioxidant system, plays an important role in scavenging reactive oxygen species and detoxification process, HCh- diet, in the present study, was found to reduce significantly GSH content of the cardiac and hepatic tissues. Therefore liver necrosis **[Abdel-Wahhab & Ali, (2003)]** and tissue damage begins when GSH stores are exhausted. In addition, reduced SOD activity was seen also, herein, in rats fed HCh- diet suggesting the inhibiting effects of hyperlipidemia on the defense system leading to damage and functional disorders in many organs including heart and liver. However, the coadminsteration of RJ to rats fed HCh- diet led to significant reduction in LP product (MDA) and an improvement in the defense system (GSH content and SOD activity) in both the cardiac and hepatic tissue. Such results support the antioxidant property of RJ **[Takeshi *et al.*, (2001)]** and its scavenging ability of free radicals **[Nagai et al., (2006)]**. RJ may protect the cardiac muscle and the hepatic tissue through their broad spectrum of biological and pharmacological properties such as hypolipidemic effect **[Vittek, (1995)]**, vasodilative and hypotensive activity **[Shinoda *et al.*, (1978)]**, as well as antioxidant effects **[Takeshi *et al.*, (2001)]** and immunomodulatory action **[Oka *et al.*, (2001)]**. Such beneficial effects are brought out through their component including proteins, vitamins, enzymes, hormones and lipid. Particularly,10 hydroxy-2- decenoic acid (10-HAD) protect from chronic diseases **[Takasu *et al.*, (1975)]** and the protein fractions have high antioxidative activity and scavenging ability against oxygen species **[Nagai & Inoue, (2004) and Nagai *et al.*, (2006)]**.

In conclusion, the biochemical results confirm the efficacy of RJ in preventing hyperlipidemia and exerting treatment and protective effects against cardiac and hepatic damage as a result of subsequent events for hypercholesterolemia.

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الملخص العربى

يهدف هذا البحث إلي دراسة تأثير المعاملة بالغذاء الملكي علي مستوي الكوليستيرول والدهون المتعلقة بأمراض القلب وتشحم الكبد في الجرذان المغذاة علي علائق عالية المحتوي من الكوليسترول وماقد يكون للإجهاد التأكسدي من دور في ذلك.

في هذه الدراسة قسمت الفئران إلي خمسة مجموعات ضمت المجموعات الضابطة والمجموعات المعاملة بالغذاء الملكي (١٠ ملجم / ١٠٠ جم من وزن الجسم) والمغذاة بالطعام العادي أو المضاف له ٠,٥% كوليسيترول (وزن/ وزن) لمدة أربعة أو ستة أسابيع . في نهاية التجربة تم سحب عينات من الدم و عينات من أنسجة الكبد والقلب لإجراء الدراسات البيوكيميائية المختلفة . وقد أثبتت النتائج أن :

١- التغذية علي علائق عالية في محتواها من الكوليستيرول أدت إلي :

- حدوث زيادة ذات دلالة معنوية فى كل أنواع الدهون بالدم وأنسجة القلب والكبد (الدهون الكلية والكوليستيرول الكلي والجلسريدات الثلاثية والدهون الفوسفورية) وكذلك في محتوي المصل من الليبوبروتينات منخفضة الكثافة ونسبتها ألي تلك عالية الكثافة، وفى المقابل قلت الليبوبروتينات عالية الكثافة وقلت نسبتها إلي الكوليستيرول الكلي كما أدت إلي زيادة ذات دلاله معنوية في نشاط إنزيمات(LDH, ALT, AST and ALP) في المصل وأنسجة القلب والكبد وكذلك في نشاط إنزيم(CK) في كل من المصل والقلب .

- حدثت زيادة معنوية في ناتج تأكسد الدهون (MDA) في كل من القلب والكبد، بينما نقص نشاط الانزيم المضاد للأكسدة (SOD) ومحتوي الجلوتاثيون المختزل (GSH).

٢- الجرذان المعاملة بالغذاء الملكي بمفرده كانت مطابقة للحيوانات في المجموعة الضابطة في معظم القياسات محل الدراسة عدا زيادة معنوية في الليبوبروتينات عالية الكثافة وكذلك نسبتها إلى الكوليستيرول الكلي في السيرم وكذلك في محتوى القلب من(SOD)، ومحتوى الكبد من(GSH). بينما أدت إلي نقص معنوي في الكوليستيرول الكلي بأنسجة القلب.

٣- أدت المعاملة بالغذاء الملكي و الكوليستيرول في نفس الوقت إلى حدوث تحسنا معنويا في كل القياسات المذكورة في اتجاه القيم الطبيعية للمجموعة الضابطة. كما أثبتت النتائج أن هذه التحسنات كانت أكثر وضوحا في الفئران المعاملة بالغذاء الملكي مع الكوليستيرول لمدة ستة أسابيع.